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ORIGINAL REPORT

Phase II Study of Erlotinib in Patients With Locally Advanced or Metastatic Papillary Histology Renal Cell Cancer: SWOG S0317

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ABSTRACT

Purpose
Patients with advanced papillary renal cell cancer (pRCC) have poor survival after systemic therapy; the reported median survival time is 7 to 17 months. In this trial, we evaluated the efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor in patients with advanced pRCC, a tumor type associated with wild-type von Hippel Lindau gene.

Patients and Methods
Patients with histologically confirmed, advanced, or metastatic pRCC were treated with erlotinib 150 mg orally once daily. A RECIST (Response Evaluation Criteria in Solid Tumors) response rate (RR) of ≥ 20% was considered a promising outcome. Secondary end points included overall survival and 6-month probability of treatment failure.

Results
Of 52 patients registered, 45 were evaluable. The overall RR was 11% (five of 45 patients; 95% CI, 3% to 24%), and the disease control rate was 64% (ie five partial response and 24 stable disease). The median overall survival time was 27 months (95% CI, 13 to 36 months). Probability of freedom from treatment failure at 6 months was 29% (95% CI, 17% to 42%). There was one grade 5 adverse event (AE) of pneumonitis, one grade 4 thrombosis, and nine other grade 3 AEs.

Conclusion
Although the RECIST RR of 11% did not exceed prespecified estimates for additional study, single-agent erlotinib yielded disease control and survival outcomes of interest with an expected toxicity profile. The design of future trials of the EGFR axis in pRCC should be based on preclinical or molecular data that define appropriate patient subgroups, new drug combinations, or potentially more active alternative schedules.

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INTRODUCTION

Renal cell cancer (RCC) accounted for approximately 50,000 new cancer occurrences per year in the United States and 13,000 deaths in 2007. Clear cell RCCs (CC-RCCs) make up approximately 75% to 80% of RCCs and have a highly variable clinical course. CC-RCCs are characterized by well-recognized genetic mutations that include abnormalities of chromosome 3p,[1] in which mutations or deletions typically involve the von Hippel Lindau (*vHL*) gene. The vHL protein is responsible for the degradation of hypoxia-inducing factor 1α (HIF-1α).[2] HIF-1α accumulation results in increased transcription of mRNA coding for the highly potent angiogenic protein, vascular endothelial growth factor (VEGF). Mutations of the *vHL* gene typically produce an accumulation of HIF-1α that results in an increased production of VEGF.[3] Overall, approximately 50% to 70% of sporadic CC-RCCs are associated with mutations or epigenetic silencing of *vHL*.[4] Recent advances in the treatment of CC-RCC have significantly changed the landscape of management of this disease.

In contrast, papillary RCC (pRCC) comprises approximately 10% to 20% of RCC occurrences.[5,6] These tumors generally do not have mutations of chromosome 3p and have wild-type *vHL* expression.[1] pRCC is thought of as resistant to immunotherapy.[6,7] Recent evidence suggests that tyrosine kinase inhibitors (TKIs), such as sorafenib and sunitinib, also have low levels of activity in pRCC compared with levels in CC-RCC.[8] There currently is no consensus as to the standard treatment for metastatic pRCC.

Work by Perera et al[9] suggested that the cytotoxic effect of antibody therapy directed against EGFR is dependent on the expression of a wild-type *vHL* gene. In these studies, clear cell and non–clear cell RCC lines were examined for responsiveness to C225, an epidermal growth factor receptor (EGFR)–directed antibody. Clear cell variants that expressed a mutated *vHL* gene demonstrated a mean 14.58% growth inhibition. In contrast, tumor cell lines (including two papillary cell lines) with wild-type *vHL* expression demonstrated a mean 42.25% growth inhibition ($P < .02$).

On the basis of the data derived from this preclinical study that demonstrated a growth inhibitory effect for two pRCC cell lines, and on the basis of the absence of effective standard therapy for the treatment of pRCC, the Southwest Oncology Group (SWOG) initiated a trial of the EGFR TKI erlotinib in patients with metastatic, histologically confirmed pRCC. This is the first prospective trial to focus on this subtype of RCC and, therefore, represents a landmark trial for the ability to study uncommon histologic variants. Comprehensive analysis of *vHL* mutational status also was performed to assess the hypothesis that wild-type *vHL* would be seen in this population.

PATIENTS AND METHODS

This multicenter, cooperative-group trial sponsored by SWOG included participation by the Eastern Cooperative Oncology Group (ECOG) and initiated accrual in April 2005. This clinical trial was approved by the institutional review boards of all participating institutions before patient enrollment occurred.

Eligibility

Eligible patients had histologically or cytologically confirmed pRCC according to central pathology review that was metastatic (M1) or unresectable (but M0). Patients had measurable disease and may not have received prior chemotherapy or immunotherapy. Prior radiation therapy was allowed (if completed at least 21 days before registration) if there was measurable disease outside the radiation port. Prior surgery was allowed, provided surgery was performed at least 28 days before registration and that recovery from all adverse effects of the surgery had occurred. A Zubrod performance score of 0 to 2 and adequate hepatic function, hematologic function, and renal function as determined by creatinine clearance were required. Patients were ineligible if they were known to be HIV positive, were unable to swallow oral medication, or had an ongoing active GI disorder that interfered with their ability to take daily oral agents. Signed informed consent was obtained for all study participants, and additional consent to submit pathology specimens was obtained for all patients who submitted tumor samples.

Pretreatment Evaluation

Pretreatment, all patients underwent screening laboratories, physical examinations, and baseline radiologic studies. Central review of previously obtained tumor biopsies was required for confirmation of pRCC diagnosis. In addition, paraffin-embedded samples were submitted for DNA analysis of *vHL* mutational status.

Treatment

Patients received erlotinib 150 mg/d orally for 28 days (ie, one cycle); the number of cycles was not prespecified and was continued until disease progression, patient refusal, unacceptable toxicity, or a treatment delay of greater than 3 weeks occurred. Patients took erlotinib each morning, 1 hour before or 2 hours after eating, and underwent monthly physical exams along with routine laboratory monitoring biweekly for the first two cycles and monthly thereafter. Baseline ophthalmologic evaluation was required, and follow-up examinations were based on ocular complaints or findings. Toxicities were assessed with the National Cancer Institute Common Toxicity Criteria, version 2.0.

Dose Modifications

Expected erlotinib toxicities included skin rash and diarrhea. Grade 2 diarrhea and skin rash did not require interruption of treatment, as these toxicities sometimes improve despite continued treatment. For unacceptable grade 2 skin rashes and diarrhea, erlotinib was held until resolution to grade 1 or better and was subsequently restarted at the same dose. If symptomatic grade 2 diarrhea and skin rash recurred and required temporary discontinuation again, treatment was held until resolution to grade 1 or better, and a dose reduction to 100 mg/d was instituted. For significant, grade 2, nonhematologic toxicity, treatment was held until resolution to grade 1 or better and was reinstituted at 100 mg/d. Patients were allowed two dose reductions to 100 mg/d and 50 mg/d. Patients who experienced intolerable toxicity or who required additional dose reductions were removed from study.

Definition of Response

All patients were assessed for response every 8 weeks with RECIST (Response Evaluation Criteria in Solid Tumors). Confirmation of partial or complete responses occurred at least 4 weeks after the response was noted. Patients who had stable disease, which was defined as a less than 20% increase or less than 30% decrease in measurable target lesions, were observed until disease progression occurred. Documented stable disease required a second assessment at least 1 month after the first that failed to demonstrate progressive disease or objective response.

Methodology for vHL, EGFR, and Human Epidermal Growth Factor Receptor 2 Analysis

Archival tumor specimens were solicited from consenting patients on this trial. Immunohistochemistry for EGFR and human epidermal growth factor receptor 2 (HER2) was performed by using Zymed antibody 31G7 (Invitrogen, Carlsbad, CA) and Dako polyclonal antibody (Catalog A0485, lot 108; Dako, Copenhagen, Denmark), respectively. Studies were conducted by using an objective and reproducible staining method that was previously reported.[10,11] This method takes into account both the intensity of staining and the percentage of stained cells. Tumor-staining intensity is scored on a scale of 0 to 4+ for multiple regions of the tumor. The percentage of stained tumor cells also is evaluated, and it ranges from 0% to 100%. The intensity is multiplied by the percent positive, and this produces a final score that ranges from 0 to 400. Immunohistochemistry analysis of HER2 levels were conducted via US Food and Drug Administration–approved methodology. Analysis of *vHL* mutations were performed by using polymerase chain reaction (PCR) assay and direct sequencing.

Statistical Considerations

The primary end point of this study was response rate (ie, confirmed and unconfirmed complete and partial responses). A two-stage design was used for patient accrual. The regimen was deemed worthy of additional study if the true probability of response was 20% or greater, and the regimen was not considered of interest if the true probability of response was 5% or less. If one or more responses were observed in the first 20 patients, an additional 20 patients were to be accrued. With 40 patients, five or more observed responders were needed to warrant additional study of this treatment, provided toxicity was reasonable. This design had a power of 92% and a significance level of .047 (using a one-sided test).

Secondary objectives included the 6-month probability of treatment failure, overall survival, and the toxicity of the regimen. Time to treatment failure was defined as the time to progression, death, symptomatic deterioration, or early discontinuation of treatment. Patients not known to have failed treatment were censored at the date of last contact. For the survival end point, patients currently alive were censored at the date of last contact. Kaplan-Meier estimates were used to calculate the 6-month probabilities of treatment failure and overall survival. With 40 patients, the probability of occurrence of any specific toxicity and 6-month treatment failure probability could be estimated to within 16%.

Another secondary objective involved investigating the association of tumor response with expression of EGFR, HER2 status, and *vHL* gene mutation status. The results obtained from this analysis were exploratory.

RESULTS

Patient Characteristics

Fifty-two patients from 27 SWOG institutions and two ECOG institutions were registered between April 2005 and December 2006. Seven patients (13%) were ineligible because of insufficient pathology material (n = 3), no measurable disease (n = 2), incorrect histology per central review (n = 1), and measurable disease not assessed within 28 days before registration (n = 1). One of the 45 eligible patients was clinically eligible but was administratively ineligible, because fewer slides were submitted than required per protocol. Central review confirmed the sample to be pRCC, and the patient was included in the primary analysis.

Six of the 45 eligible patients had baseline tissue samples submitted for central pathology review that were lost in transit, and central pathology review could not be conducted. Per protocol, submission of these materials by the institution was sufficient for eligibility. A decision was made to include all six patients in the final analysis (ie, intention-to-treat analysis). Two of these six patients had institutional pathology reports that documented papillary histology, whereas no institutional pathology reports were available for review for four patients. Patient characteristics are listed in Table 1.

Treatment Received

Thirty-six of the 45 patients received a minimum of two cycles of therapy and were assessed for response. Seven patients discontinued therapy before the first response assessment for the following reasons: patient withdrawal (n = 1), death as a result of RCC (n = 1), disease progression (n = 4), and switch to another treatment (n = 1). Two patients received more than two cycles of treatment but were not assessable for response for reasons related to evaluation errors, and these patients are included among the five presumed nonresponders in the calculation of the response probability.

Table 1. Demographic and Clinical Characteristics of Eligible and Evaluable Patients Registered to S0317

Characteristic	Patients (N = 45) No.	%
Age, years		
Median	63	
Range	27-82	
Sex		
Male	33	73
Female	12	27
Ethnicity		
White	35	78
African American	7	16
Asian	1	2
Native American	1	2
Unknown	1	2
Hispanic origin		
Yes	0	0
No	43	96
Unknown	2	4
Zubrod score		
0	34	76
1	8	18
2	1	2
Unknown	2	4

Efficacy

Median follow-up for surviving patients was 21 months (range, 9 to 42 months). There were four confirmed partial responses and one unconfirmed partial response, which together provided an overall response probability of 11% (95% CI, 3% to 24%). Sites of response included lymph nodes, soft tissue, adrenal gland, kidney, liver, and pelvis. Five patients had disease assessment data submitted that was inadequate for response assessment, were assumed to be nonresponders, and were included in the calculation of the response probability. Twenty-four additional patients had stable disease as the best response, and this provided an overall disease control rate (ie, partial response plus stable disease) of 64%. The 6-month probability of freedom from treatment failure was 29% (95% CI, 17% to 42%). Estimates for the proportion of patients who were stable or better at 2, 4, and 6 months of treatment are 71%, 44%, and 31%, respectively. A graph of time to treatment failure is shown in Figure 1. The 6-month overall survival was estimated as 87% (95% CI, 72% to 94%). Median survival was estimated to be 27 months (95% CI, 13 to 36 months). A graph of overall survival is presented in Figure 2.

Toxicity

Among the 45 patients evaluable for toxicity, the majority of the toxicities seen were grades 1 and 2 and included diarrhea, rash, anorexia, and fatigue. One patient had grade 5 pneumonitis, and one patient had a grade 4 pulmonary embolism. Both were possibly related to erlotinib treatment. Nine patients had grade 3 toxicities, and the most prevalent of these were anorexia (n = 2) and rash (n = 2). Another patient had grade 3 pneumatosis of the small bowel that was attributed to protocol treatment.

vHL, *EGFR, and HER2 Tumor Analysis*

The *vHL* analysis was performed on 35 of 37 specimens received (because of inadequate tissue in two patients). Two *vHL* mutations were detected: one each in exons 1 and 2. In the first, the mutation was in codon 130 and had a base change of GTT to CTT, which resulted in

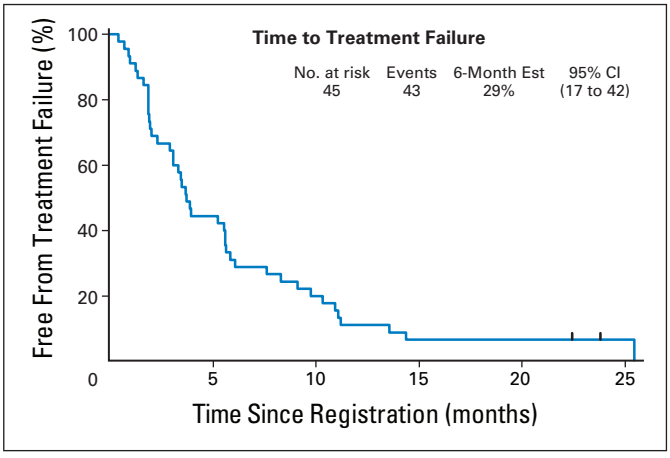

Fig 1. Time to treatment failure for evaluable patients registered to S0317. Est, estimate.

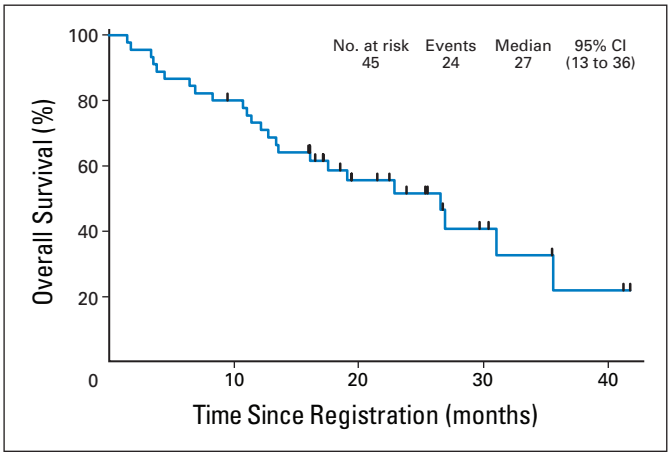

Fig 2. Overall survival for eligible and evaluable patients registered to S0317.

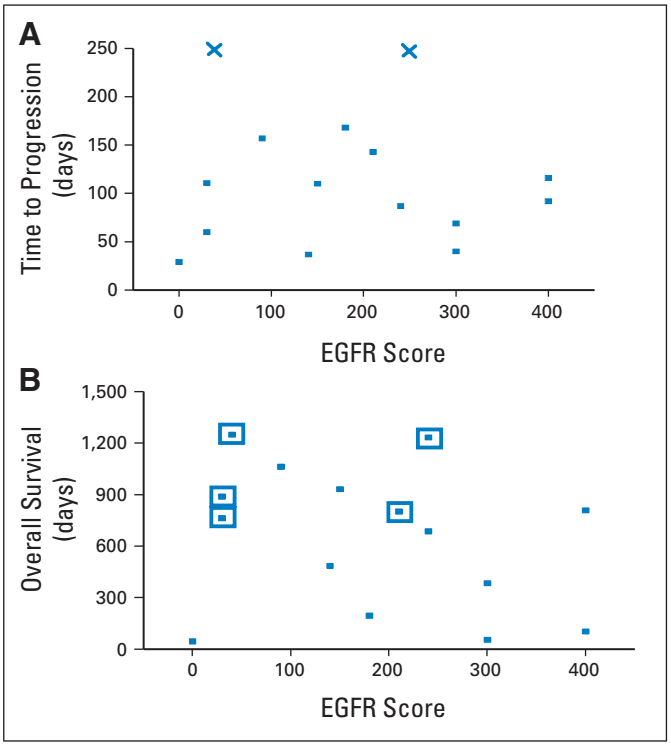

Fig 3. Epidermal growth factor receptor (EGFR) score by immunohistochemistry and (A) time to progression (TTP) or (B) overall survival. (blue X) patients with extended TTP (1,250 and 763). (blue open squares) patients are still alive.

an amino acid substitution of valine to leucine. The other base change was GAG to GAC, which resulted in an amino acid substitution of glutamine to aspartate.

Twenty-two specimens were stained by immunohistochemistry for EGFR and HER2 on the basis of tissue availability after *vHL* mutational analysis. Four specimens had inadequate tissue for EGFR staining, and five specimens were insufficient for HER2. All but one specimen stained positive for EGFR (17 of 18 specimens), and eight (44%) of 18 specimens scored greater than 200. Only one of 17 specimens stained positive for HER2 with a score of 140; this specimen also scored greater than 200 for EGFR. This data is listed in Table 2 and Figure 3. The patient with an EGFR-negative tumor experienced rapid progression and died 44 days after initiation of treatment. For patients who had positive scores, no associations or patterns were observed between EGFR score or staining intensity with time to progression or overall survival. Fifteen viable specimens corresponded to patients who also were assessable for response. Five of these had progressive disease, and 10 had stable disease or better (stable disease, n = 9; confirmed partial response, n = 1). The analysis of these fifteen specimens is presented in Table 3. The *vHL* mutations were present in two patients who had best response of stable disease. The only patient with HER2 expression had 70% of cells positive and experienced progression on study. Thirty percent of patients who had stable disease or

Table 2. EGFR Score and Survival Outcomes

	Outcomes			
			Overall Survival	
EGFR Score	Response	Time to Progression (days)	Result	Length of Time (days)
0	POD	29	Death	44
30	POD	60	Alive	763
30	STA	111	Alive	888
40	STA	Progression not reached	Alive	1,249
90	PR	157	Alive	1,062
140	POD	37	Death	484
150	STA	110	Death	931
180	STA	168	Death	194
210	STA	143	Alive	800
240	STA	87	Death	686
240	STA	763	Alive	1,233
300	POD	40	Death	53
300	POD	69	Death	383
400	STA	92	Death	102
400	STA	116	Death	808

Abbreviations: EGFR, epidermal growth factor receptor; POD, progression of disease; STA, stable; PR, partial response.

Table 3. Summary of Correlative Studies in 15 Eligible Patients With Response Assessment and Viable Tumor Samples

Variable	Best RECIST Response: Increasing Disease (n = 5) No.	%	Stable or Better (n = 10) No.	%
EGFR score, intensity × percent*				
0-99	2	40	3	30
100-199	1	20	2	20
200-299	0	0	3	30
300-400	2	40	2	20
vHL mutation†	0	0	2	20
HER2 score, intensity × percent‡				
0	4	80	10	100
> 0	1	20	0	0

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; EGFR, epidermal growth factor receptor; vHL, von Hippel Lindau gene; HER2, human epidermal growth factor receptor 2.
*Score for confirmed partial response is 90.
†Both patients who had mutations had best response of stable disease.
‡Patient who had a score of 140 had increasing disease.

better had a score in the range of 200 to 299, as opposed to none of the patients with increasing disease.

DISCUSSION

pRCC represents a distinct subset of patients with kidney cancer. Patients with pRCC often present with small, frequently multifocal disease and tend to have a somewhat better prognosis after nephrectomy compared with patients who had CC-RCC.[12] In contrast, however, patients with pRCC who develop metastases have fewer treatment options. pRCC is divided into two distinct subtypes—type I pRCC, which is often associated with mutation or abnormal activation of the c-met receptor, and type II papillary RCC tumors, which have mutations of fumarate hydratase and are associated with a syndrome of hereditary leiomyomatosis. In this trial, we did not test for tumor grade or for the subtype of pRCC.

A number of studies of EGFR inhibitors have been carried out in RCC.[13-17] Most of these either included all RCC histologies or treated only patients with CC-RCC. Response rates have routinely been in the range of approximately 10%, and there have been no biologic studies to determine which patients may benefit from this targeted therapy. An initial phase II study of erlotinib combined with bevacizumab in patients who had CC-RCC suggested clinical activity,[18] but a randomized, phase II study was terminated because of futility when it became apparent there was no benefit to the combination of the two agents compared with bevacizumab alone.[19] Our trial sought to define the activity of erlotinib in pRCC, given preclinical data to suggest that EGFR inhibition may have activity in this subset of RCC.

As expected, erlotinib was generally well tolerated, and toxicities were associated with the known safety profile of the drug, including a skin rash and diarrhea. Rare grades 4 or 5 toxicities were seen, and most patients tolerated the treatment without the need for dose reductions.

Objective responses were seen in five patients who had pRCC, including one patient for whom we were unable to centrally confirm the histology. In addition to the patients who responded, 24 patients had stable disease; for these patients, the 6-month rate of freedom from treatment failure was 29%, and the median overall survival was 27 months. Although this data suggests that erlotinib therapy in this patient population resulted in an interesting impact on the expected outcome for this subtype of RCC, additional preclinical studies are needed to better define the molecular pathways potentially associated with these benefits.

Importantly, erlotinib is a specific EGFR TKI and does not affect other potential target receptors in this disease, such as the c-met receptor. This biologic premise would suggest again that the HER pathway may be an independently important one in the progression of pRCC and that future combinations of EGFR/pan-HER inhibitors with therapies that target the c-met pathway may have the potential to exert antitumor activity via complementary pathways. Formal assessment of this hypothesis in laboratory models of both type I and type II pRCC would aid in determining the relevance of this consideration.

To our knowledge, this is the largest study to date to target pRCC. We performed clinical correlation studies of the *vHL* pathway to confirm that pRCC do not express mutations of the *vHL* gene. In fact, two histologically confirmed pRCC tumors had mutations of the *vHL* gene. It is unclear whether these tumors represent an overlap with CC-RCC or, perhaps, a mixed tumor histology. Among the remaining tumors available for analysis, there were no mutations of the *vHL* gene to confirm that the vast majority of pRCC have wild-type *vHL* and that therapies to target this signaling pathway may be, therefore, less effective in this subgroup of RCC than in the CC-RCC population.

Because we appreciated the lack of correlation of EGFR expression with response to EGFR inhibitors in other diseases, we did not require EGFR expression for eligibility to this study. Exploratory evaluation of EGFR expression failed to identify an association between EGFR immunohistochemical staining and response, time to progression, or overall survival. This finding suggests that mutational status, receptor amplification, or differential intracellular signaling mechanisms may play a significant role in the prediction of clinical benefit from EGFR-directed therapies in this disease. These findings are consistent with findings reported about EGFR therapy in other cancers.[20] HER2 staining also did not correlate with outcome. Fewer samples were available for clinical correlation for this end point, which may have compromised the ability to reach definitive conclusions. It is important to note, however, that recent evidence indicates that HER3 expression may play a role in escape from HER-family tyrosine kinase inhibition; hence, assessment of this HER family member may be important in future assessments.[21]

In conclusion, we have demonstrated that EGFR inhibition has the ability to induce stable disease and a low number of objective responses in patients with pRCC. Given that the majority of patients did not have a *vHL* mutation, this feature cannot be used to select patients for future study. A better understanding of the molecular pathobiology in this form of RCC and additional preclinical studies to define potential combinations are warranted before moving forward with additional trials of this or similar agents in pRCC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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REFERENCES

1. Gnarra J, Lerman M, Zbar B, et al: Genetics of renal cell carcinoma and evidence for a critical role for von Hippel-Lindau in renal tumorigenesis. Semin Oncol 22:3-8, 1995

2. Linehan M: Identification of the Von Hippel Lindau (VHL) gene: Its role in renal cancer. JAMA 273:564-570, 1995

3. Levy A, Levy N, Iliopoulos O, et al: Regulation of vascular endothelial growth factor by hypoxia and its modulation by the von Hippel-Lindau tumor suppressor gene. Kidney Int 51:575-578, 1997

4. Igarashi H, Esumi M, Ishida H, et al: Vascular endothelial growth factor overexpression is correlated with von Hippel-Lindau tumor suppressor gene inactivation in patients with sporadic renal cell carcinoma. Cancer 95:47-53, 2002

5. Delahunt B, Eble J, McCredie M, et al: Morphologic typing of papillary renal cell carcinoma: Comparison of growth kinetics and patient survival in 66 cases. Hum Pathol 32:590-595, 2001

6. Motzer R, Bacik J, Mariani T, et al: Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear cell histology. J Clin Oncol 20:2376-2381, 2002

7. Upton M, Parker R, Youmans A, et al: Histologic predictors of renal cell carcinoma response to interleukin-2 based therapy. J Immunother 28:488-495, 2005

8. Choueiri T, Plantade A, Elson P, et al: Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. J Clin Oncol 26:127-131, 2008

9. Perera A, Kleymenova E, Walker C: Requirement for the von Hippel-Lindau tumor suppressor gene for functional epidermal growth factor receptor blockade by monoclonal antibody c225 in renal cell carcinoma. Clin Cancer Res 6:1518-1523, 2000

10. Tsao M, Sakurada A, Cutz J, et al: Erlotinib in lung cancer: Molecular and clinical predictors of outcome. N Engl J Med 353:133-144, 2005

11. Cappuzzo F, Hirsch F, Rossi E, et al: Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst 97:643-655, 2005

12. Beck S, Patel M, Snyder M, et al: Effect of papillary and chromophobe cell type on disease free survival after nephrectomy for renal cell carcinoma. Ann Surg Oncol 11:71-77, 2004

13. Dawson N, Guo C, Zak R, et al: A phase II trial of gefitinib (Iressa, ZD 1839) in stage IV and recurrent renal cell carcinoma. Clin Cancer Res 10:7812-7819, 2004

14. Jermann M, Stahel R, Salzberg M, et al: A Phase II, open-label study of gefitinib (IRESSA) in patients with locally advanced, metastatic, or relapsed renal-cell carcinoma. Cancer Chemother Pharmacol 57:533-539, 2006

15. Motzer R, Amato R, Todd M, et al: Phase II trial of antiepidermal growth factor receptor antibody C225 in patients with advanced renal cell carcinoma. Invest New Drugs 21:99-101, 2003

16. Ravaud A, Hawkins R, Gardner J, et al: Lapatinib versus hormonal therapy in patients with advanced renal cell carcinoma: A randomized phase II clinical trial. J Clin Oncol 26:2285-2291, 2008

17. Rowinsky E, Schwartz G, Gollob J, et al: Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor antibody in patients with metastatic renal cell cancer. J Clin Oncol 22:3003-3015, 2004

18. Hainsworth J, Sosman J, Spigel D, et al: Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib. J Clin Oncol 23:7889-7896, 2005

19. Bukowski R, Kabbinavar F, Figlin R, et al: Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. J Clin Oncol 25:4536-4541, 2007

20. Marks J, Broderick S, Zhou O, et al: Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. J Thorac Oncol 3:111-116, 2008

21. Sergina N, Rausch M, Wang D, et al: Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. Nature 445:437-441, 2007